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Abstract: Aims The purpose of the current trial was to test the hypothesis that breathing oxygen-enriched air increases exercise performance of patients with pulmonary arterial or chronic thrombo-embolic pulmonary hypertension (PAH/CTEPH) and to investigate involved mechanisms. Methods and results Twenty-two patients with PAH/CTEPH, eight women, means ± SD 61 ± 14 years, resting mPAP 35 ± 9mmHg, PaO2 ambient air >7.3 kPa, underwent four bicycle ergospirometries to exhaustion on different days, while breathing oxygen-enriched (FiO2 0.50, hyperoxia) or ambient air (FiO2 0.21, normoxia) using progressively increased or constant load protocols (with 75% maximal work rate under FiO2 0.21), according to a randomized, sham-controlled, single-blind, cross-over design. ECG, pulmonary gas-exchange, arterial blood gases, cerebral and quadriceps muscle tissue oxygenation (CTO and QMTO) by near-infrared spectroscopy were measured. In ramp exercise, maximal work rate increased from 113 ± 38 W with normoxia to 132 ± 48 W with hyperoxia, mean difference 19.7 (95% CI 10.5-28.9) W, $P < 0.001$. Constant load exercise endurance increased from 571 ± 443 to 1242 ± 514 s, mean difference 671 (95% CI 392-951) s, $P < 0.001$. At end-exercise with hyperoxia PaO2, CTO, QMTO, and PaCO2 were increased, and ventilatory equivalents for CO2 were reduced while the physiological dead space/tidal volume ratio remained unchanged. Conclusion In patients with PAH/CTEPH, breathing oxygen-enriched air provides major increases in exercise performance. This is related to an improved arterial oxygenation that promotes oxygen availability in muscles and brain and to a reduction of the excessive ventilatory response to exercise thereby enhancing ventilatory efficiency. Patients with PAH/CTEPH may therefore benefit from oxygen therapy during daily physical activities and training. Trial registration clinicaltrials.gov Identifier: NCT01748474.

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Conclusion In patients with PAH/CTEPH, breathing oxygen-enriched air provides major increases in exercise performance. This is related to an improved arterial oxygenation that promotes oxygen availability in muscles and brain and to a reduction of the excessive ventilatory response to exercise thereby enhancing ventilatory efficiency. Patients with PAH/CTEPH may therefore benefit from oxygen therapy during daily physical activities and training.

Trial registration clinicaltrials.gov Identifier: NCT01748474.

Keywords Pulmonary hypertension • Oxygen therapy • Exercise • Precapillary pulmonary hypertension

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Introduction

The major forms of precapillary pulmonary hypertension (PH), pulmonary arterial hypertension (PAH) and chronic thrombo-embolic PH (CTEPH), are characterized haemodynamically by a mean pulmonary artery pressure (mPAP) of ≥25mmHg along with a pulmonary artery wedge pressure (PAWP) of ≤15 mmHg at rest.[1] PAH and CTEPH cause dyspnea, impaired exercise performance and are associated with reduced quality of life and survival.[1–3] The symptoms and exercise limitation in patients with precapillary PH have been attributed to several pathophysiologic mechanisms. A typical finding in PAH/CTEPH is an excessive ventilatory response to exercise associated with high ventilatory equivalents for oxygen uptake and carbon dioxide (CO_2) output.[4] This has been attributed to an increased chemosensitivity, sympathetic nervous system activation and increased physiological dead space.[4,5] Further, an inadequate increase in cardiac output during exercise causes early lactic acidosis with increased CO_2 production relative to oxygen consumption thereby increasing respiratory drive and ventilatory requirements.[6,7] A low cardiac output also results in a reduced mixed venous oxygen saturation which, together with right-left shunts through a patent foramen ovale in some patients, may lead to severe arterial hypoxaemia during exercise that further stimulates ventilation and worsens PH by hypoxic pulmonary vasoconstriction.[7] As a consequence, oxygen delivery to the muscles, the brain and other organs is reduced thereby limiting exercise capacity.[6,8–10]

The treatment of precapillary PH includes pulmonary endarterectomy in selected patients with CTEPH[11,12] and PH-targeted medication or lung transplantation in patients with PAH and post-operatively persisting or inoperable CTEPH and supportive measures such as diuretics and training.[1,13,14] Continuous long-term oxygen therapy is recommended as a supportive measure if resting arterial partial pressure of oxygen (PaO_2) is <8 kPa and when there is symptomatic benefit and correctable oxygen desaturation during exercise but these recommendations are not based on robust evidence. In a systematic search of the literature we have identified only one randomized, controlled trial evaluating efficacy of oxygen therapy in precapillary PH.[15] It revealed that one week of nocturnal supplemental oxygen therapy improved the 6-minute walk distance (6MWD) in patients with PAH/CTEPH in comparison to sham-oxygen therapy. Since oxygen therapy is widely used as an adjunct to medical therapy in PAH/CTEPH-patients further studies evaluating its efficacy are needed. The purpose of the current randomized, sham-controlled trial was therefore to test the hypothesis that breathing oxygen-enriched air ($FiO_2 = 0.50$) increases exercise performance of patients with PAH or CTEPH, and to evaluate the involved physiological mechanisms.

Methods

Study design

This randomized, sham-controlled, single-blinded, cross-over trial comprises two consecutive test sequences evaluating efficacy of hyperoxia in improving exercise performance in patients with PAH or CTEPH using progressive or constant load exercise protocols, respectively. Participants gave written informed consent. The study was approved by the institutional ethics committee (KEK 2012-0251) and registered at ClinicalTrials.gov (NCT01748474).

Participants

Consecutive patients seen at our clinic between June 2014 and January 2015 with PAH or CTEPH diagnosed according to current guidelines,[1] who were stable on PH-targeted drug therapy and had a resting PaO_2 ≥7.3 kPa but arterial oxygen desaturation during exercise were invited to participate. The diagnosis was based on a compatible history and right heart catheterization showing a mPAP ≥25 mmHg, a PAWP ≤15 mmHg. A thorough evaluation including history, ECG, echocardiography, thoracic computed tomography, ventilation perfusion scan, pulmonary angiography, blood tests for liver function, HIV and rheumatic diseases were performed as appropriate to confirm the diagnosis and classify PH. Patients with left heart or lung disease-associated PH, miscellaneous forms, resting PaO_2 <7.3 kPa, unstable condition or contraindication for ergometry were excluded.

Interventions

Patients underwent four cycle exercise tests, on four separate occasions, a few days apart. The first two tests were performed with a progressive ramp protocol to exhaustion with work rate increments of 10–20 W/min to achieve an exercise duration of 8–12 min, cycling rate was 50–60 rpm.[16] Patients were breathing either ambient air (normoxia, FiO_2 0.21) or oxygen-enriched air (hyperoxia, FiO_2 0.50), in randomized order. They breathed through a mouthpiece connected to the flow sensor of a metabolic unit (Ergostick, Geratherm Medical, Gschwenda, Germany) and a two-way valve (Hans Rudolph, Shawnee, USA). The inlet of the valve was connected to a gas-mixing device set to provide either normoxia or hyperoxia (Altitrainer, Nyon, Switzerland). The second two exercise tests were performed with constant load to exhaustion at 75% of individual maximal work rate (W_{max}) achieved during normoxia. Using the same equipment as for ramp tests, patients were breathing normoxia or hyperoxia in randomized order.

Assessments

At the screening visit, the World Health Organization functional class (WHO-FC) was recorded, and a clinical examination, 6MWD test and spirometry were performed.

During exercise tests respiratory gas exchange was recorded with the metabolic unit calibrated before each test. Breath-by-breath values for minute ventilation ($V'E$), breath rate, tidal volume, CO_2 output ($V'CO_2$), and derived variables were recorded. Oxygen uptake is not reported for tests with hyperoxia because accuracy of the O_2-sensor outside the calibration range of FO_2 0.16–0.21 could not be verified. Heart rate was derived from a 4-lead ECG, blood pressure by automated arm-cuff measurements. Finger pulse oximetry (SpO_2) and regional tissue oxygenation of the brain and quadriceps muscle were also recorded. To this end, a near-infrared-spectroscopy sensor (Hamamatsu, NIRO-200NX, Shizuoka, Japan) was attached with adhesive tape high on the forehead to record cerebral tissue oxygen saturation (CTO) as ratio of oxygenated/(oxygenated + deoxygenated) haemoglobin concentrations in per cent. A second sensor placed parallel to the long axis of the right vastus lateralis, mid-distance between the great trochanter and the lateral epicondyle, recorded quadriceps muscle tissue oxygen saturation (QMTO).[17–19]

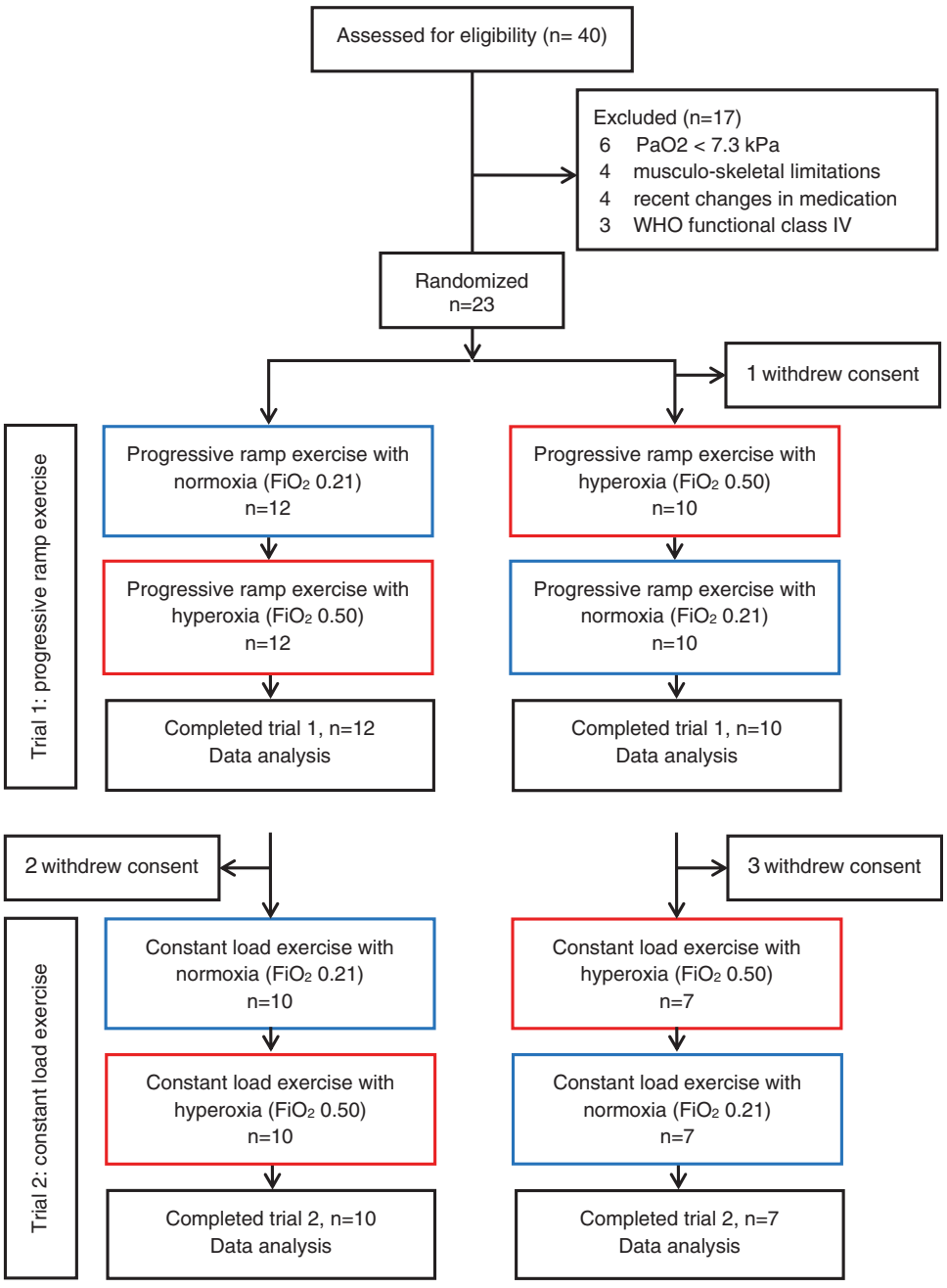

Figure 1 Study design with patient flow in trials with progressive ramp exercise (Trial 1) and constant load exercise (Trial 2) at 75% of maximal work rate achieved with room air. Blue and red frames mark trials with FiO_2 0.21 and 0.50, respectively.

Physiologic variables were recorded breath-by-breath and averaged over successive 30-s intervals. Maximal physiologic variables (end-exercise) were defined as mean values over the final 30 s of exercise. The ventilatory equivalent for $V'CO_2$ was calculated as $V'E/V'CO_2$ at end-exercise and as slope over the entire duration of ramp exercise.[20] The physiological dead space fraction (VD/VT) was computed from arterial and expiratory PCO_2.[16] To illustrate effects of hyperoxia on the ventilatory efficiency, $V'E/V'CO_2$ ratios were plotted vs. corresponding values of $PetCO_2$. The rearranged alveolar gas equation ($V'E/V'CO_2 = a/PetCO_2*(1-VD/VT)$ was fitted to these data points (a = constant).[21] Heart rate reserve was calculated as 220 minus age minus heart rate at end-exercise; ventilatory reserve as 40xFEV1 minus $V'E$ at end-exercise. Reference values for W_{max} and $V'O_2max$ were those of Glaser *et al.*[22]

Outcomes and sample size

Primary outcomes were the change in W_{max} during progressive ramp tests (trial 1) and the change in endurance during constant load tests (trial 2) induced by hyperoxia vs. normoxia, respectively. To our knowledge, the minimal important difference in W_{max} during submaximal exercise has not been determined for patients with PH. Therefore, according to clinical experience, we assumed a difference in W_{max} of 10 W (with a SD of 12 W for repeated tests) or an effect size of at least 0.8 (large) as clinically important.[23,24] Based on these premises we aimed at including at least 20 participants accounting for possible dropouts to achieve a power of 0.9 (alpha 0.05). Secondary outcomes were physiologic variables at end-exercise and at corresponding submaximal workloads (isoload/isotime).

Randomization and blinding

Randomization was performed by letting participants draw a sealed envelope from a set of envelopes containing balanced test sequences. Participants were blinded to the inhaled oxygen concentration.

Data analysis and statistics

Data are summarized as means ± SD. As the main purpose of the study was to evaluate efficacy of hyperoxia in enhancing performance of patients applying this treatment during exercise, the primary analysis was performed according to the per protocol principle in participants completing corresponding tests both in normoxia and hyperoxia; an intention to treat analysis is also presented for the main outcomes conservatively assuming zero difference in outcomes between both conditions. Data from tests with hyperoxia were compared with those with normoxia in terms of the mean difference and 95% confidence intervals. Data from progressive workloads during both ramp tests were compared by computing means over successive fractions of maximal exercise time during normoxia, i.e. over the periods from 1–10%, 11–20%, etc., up to 91–100% exercise time in normoxia, and over identical time periods in tests with hyperoxia. Data from constant load tests in hyperoxia and normoxia were compared at end-exercise and at isotimes. Isotime refers to the time under hyperoxia that corresponds to the time of end-exercise under normoxia. Linear regression analyses were used to explore whether physiologic changes induced by hyperoxia were correlated with patient characteristics. Variables that were significant in univariate analysis were entered into a multivariate analysis. Significance was assumed at $P < 0.05$.

Table 1 Patient characteristics

Number of participants (female)	22 (8)
Age, years	61 ± 14
Body mass index, kg/m^2	27.1 ± 6.0
New York Heart association functional class (II, III)	11 (50%), 11 (50%)
6-min walk distance, m	540 ± 83
SpO_2 at rest, %	95 ± 3
SpO_2 at end of 6-min walk, %	89 ± 5
Classification	
Pulmonary arterial hypertension	11 (50%)
• Idiopathic	8 (36%)
• Connective tissue disease related	2 (9%)
• Porto-pulmonary	1 (5%)
Chronic thrombo-embolic pulmonary hypertension	11 (50%)
Treatment	
Endothelin receptor antagonist	9 (41%)
Phosphodiesterase-5-inhibitor	5 (23%)
Soluble guanylate-cyclase simulator	4 (18%)
Combination therapy	2 (9%)
Nocturnal oxygen therapy	1 (5%)
Right heart catheter data and systemic blood pressure	
Mean pulmonary artery pressure, mmHg	35 ± 9
Pulmonary artery wedge pressure, mmHg	11 ± 3
Right atrial pressure, mmHg	8 ± 4
Cardiac index, l/min/m^2	2.9 ± 0.6
Pulmonary vascular resistance, WU	4.7 ± 2.5
Mixed venous oxygen saturation, %	68 ± 5
Heart rate, bpm	80 ± 18
Systemic blood pressure, systolic	128 ± 16
and diastolic, mmHg	79 ± 9
Lung function	
Forced expiratory volume in 1 s (FEV1), % predicted	91 ± 21
Forced expiratory volume (FVC), % predicted	97 ± 23
FEV1/FVC	76 ± 7
Total lung capacity, % predicted	95 ± 16
Diffusion capacity for carbon dioxide, % predicted	69 ± 22
Ramp protocol	
10, 15, 20, 25 W/min, *n*	10/11/0/1

Date are presented as mean ± SD, numbers and per cent
SpO_2, pulse oximetry.

Results

Patients

The patient flow is shown in *Figure 1*. Twenty-three patients were randomized, one of them withdrew consent before undergoing any test; five participants completing ramp tests refused to participate in subsequent constant load tests because of lack of time. Therefore, data from ramp tests were available for in 22 patients, data from constant load tests in 17 patients. Patients were in WHO-FC 2 or 3, mean resting mPAP was 35 ± 9 mmHg, resting SpO_2 was 95 ± 3% (*Table 1*).

Progressive ramp tests under normoxia and hyperoxia

Table 2 and *Figures 2–4* summarize the results of maximal ramp tests. In normoxia W_{max} was moderately reduced compared with predicted normal values (113 ± 38 W, 71 ± 18% predicted). Hyperoxia increased W_{max} significantly to 132 ± 48 W, corresponding to a mean change (95% CI) of +19.7 (10.5 to 28.9) W, $P < 0.001$ (*Figure 2*) and

Table 2 Maximal ramp bicycle exercise under normoxia and hyperoxia

	Ambient air FiO_2 0.21, Normoxia End-exercise	Oxygen enriched air, FiO_2 0.50, Hyperoxia			
		Isotime corresponding to end-exercise time under normoxia	*P*-value	End-exercise	*P*-value
Work rate, W	113 ± 38	113 ± 38	NA	132 ±48	<0.001
Work rate, % predicted W_{max}	71 ± 18	71 ± 18		81 ±19	<0.001
Endurance, s	432 ± 111	432 ± 111	NA	525 ±136	0.001
Heart rate, bpm	130 ± 8	125 ± 18	<0.001	136 ±21	<0.001
Heart rate reserve, bpm	27 ± 20	35 ± 19	<0.001	22 ±19	<0.001
Minute ventilation ($V'E$), l/min	62 ± 17	53 ± 13	<0.001	65 ±18	0.315
Breathing reserve, % MVV	42 ± 15	51 ± 14	0.001	40 ±12	0.504
Tidal volume, l	2.1 ± 0.7	2.1 ± 0.7	0.414	2.1 ±0.7	0.498
Breath rate, 1/min	32 ± 10	27 ± 10	<0.001	32 ±11	0.781
Oxygen uptake ($V'O_2$), l/min	1.4 ± 0.4	NA	NA	NA	NA
$V'O_2$, % predicted	75 ± 15				
Carbon dioxide output ($V'CO_2$). l/min	1.5 ± 0.5	1.5 ± 0.4	0.214	1.8 ± 0.6	<0.001
$V'E/V'CO_2$ slope	42.3 ± 10.6	NA	NA	36.2 ± 9.2	<0.001
$V'E/V'CO_2$ at end-exercise	40.8 ± 8.7	35.7 ± 6.5	<0.001	36.9 ± 7.4	<0.001
Death-space fraction (*VD*/*VT*)	0.40 ± 0.12	NA	NA	0.42 ± 0.09	0.310
End-tidal PCO_2, kPa	3.9 ± 0.8	4.4 ± 0.8	<0.001	4.4 ± 1.1	<0.001
Pulse oximetry (SpO_2), %	90 ± 6	99 ± 1	<0.001	98 ± 2	<0.001
Cerebral tissue SO_2, (CTO), %	61 ± 9	72 ± 7	0.001	71 ± 7	0.002
Quadriceps SO_2, (QMTO), %	61 ± 8	65 ± 10	0.001	65 ± 11	0.002
Arterial pH	7.38 ± 0.05	NA	NA	7.32 ± 0.04	<0.001
PaO_2, kPa	8.8 ± 2.5	NA	NA	32.1 ± 7.3	<0.001
$PaCO_2$, kPa	4.8 ± 0.6	NA	NA	5.4 ± 0.7	0.001
SaO_2, %	89.9 ± 7.9	NA	NA	99.4 ± 1.0	0.001
Arterial lactate, mmol/l	4.8 ± 2.1	NA	NA	5.4 ± 2.1	0.522
Arterial bicarbonate, mmol/l	21.3 ± 1.9	NA	NA	21.1 ± 1.9	0.950
Borg CR10 dyspnea score	5.8 ± 2.0	NA	NA	5.1 ± 1.9	0.064
Borg CR10 Leg discomfort score	3.7 ± 2.4	NA	NA	4.2 ± 2.3	0.459

Means ± SD, $n = 22$, primary outcome in bold. Individual values were averaged over 30 s; in tests with oxygen enriched air (FiO_2 0.50) isotime refers to the time of end-exercise in normoxia (FiO_2 0.21).
MVV, maximal voluntary ventilation; SaO_2, arterial oxygen saturation by co-oximetry; NA, not available.

thus 18 (8 to 29)%. 16/22 patients (73%) increased W_{max} by ≥5%, 13/22 patients (59%) by ≥10%. Compared with normoxia, maximal heart rate and $V'CO_2$ were higher under hyperoxia while $V'E$ was unchanged so that $V'E/V'CO_2$ at end-exercise and the $V'E/V'CO_2$ slope were significantly reduced (*Table 2*, *Figures 2* and *3*). To further explore the mechanisms responsible for the improved ventilatory efficiency pairs of $V'E/V'CO_2$ ratios at end-exercise during tests under normoxia and hyperoxia, respectively, were plotted vs. the corresponding pairs of end-tidal PCO_2. This analysis revealed that hyperoxia shifted the $V'E/V'CO_2$ ratio to a more favourable position on the line defined by the rearranged alveolar gas equation (*Figure 3*). As *VD*/*VT* ratios were similar under normoxia and hyperoxia (*Table 2*) the $V'E/V'CO_2$ ratios were reduced mainly by the higher alveolar PCO_2 rather than by a reduction in *VD*/*VT*. Hyperoxia increased SpO_2 and both the CTO and QMTO at maximal exercise. Arterial blood gas analysis at maximal exercise revealed a major increase in SaO_2 and PaO_2 but a lower pH and a higher $PaCO_2$ under hyperoxia vs. normoxia (*Table 2*). There was a trend towards reduced dyspnea at end-exercise while leg fatigue was perceived as similar under hyperoxia and normoxia (*Figure 2*). An intention to treat analysis including all randomized patients and entering 0 difference for missing values revealed principally the same results as the per protocol analysis, i.e. a mean increase in W_{max} by hyperoxia vs. normoxia of 18.8 W (95% CI 9.9–27.8, $P < 0.001$).

Comparisons of variables during progressive ramp exercise at corresponding submaximal isoloads (*Figure 4*) revealed that hyperoxia was associated with lower heart rates, $V'E$ and $V'CO_2$ compared with normoxia. A drop in SpO_2 towards end of exercise was prevented by hyperoxia and a drop in CTO was delayed until near maximal exercise.

Univariable linear regression analysis revealed that only male sex (coefficient 18.6, 95% CI 0.9–36.2, $P = 0.040$) and the 6MWD (coefficient 0.13, 95% CI 0.03–2.3, $P = 0.012$) were significantly correlated with the increase in W_{max} under hyperoxia (Supplementary material online, *Table S1*). No such correlation existed for various other

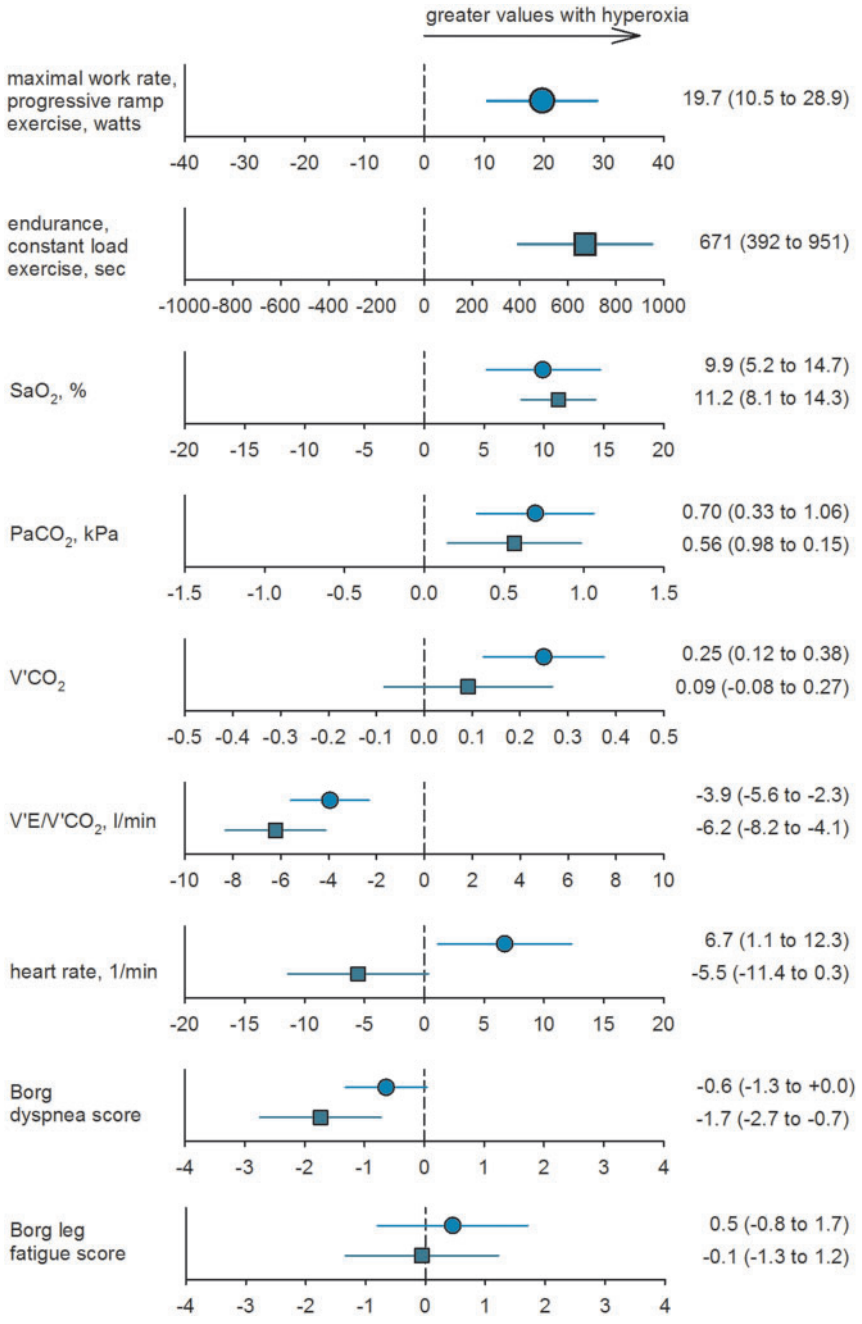

Figure 2 Changes in exercise variables induced by hyperoxia. Mean differences in corresponding variables measured during hyperoxia minus normoxia with 95% confidence intervals are displayed for progressive ramp exercise (blue circles and lines) and for constant load exercise (green squares and lines). Positive differences correspond to greater values during tests with hyperoxia. $V'CO_2$ = CO_2 output; $V'E/V'CO_2$ = ventilatory equivalent for $V'CO_2$ at end-exercise.

physiologic variables and the PH class (PAH, CTEPH). In multivariable regression analysis including sex and 6MWD, only 6MWD remained a significant predictor of the increase in W_{max} under hyperoxia (coefficient 0.11, 95% CI 0.01–0.21, P = 0.038) (Supplementary material online, *Table S1*).

Constant load exercise under hyperoxia vs. normoxia

Constant load at 75% W_{max} (normoxia) corresponded to a work rate of 86 W (range 50–155). Hyperoxia increased endurance from a mean value of 571 s in normoxia to 1242 s, i.e. a value more than twice as

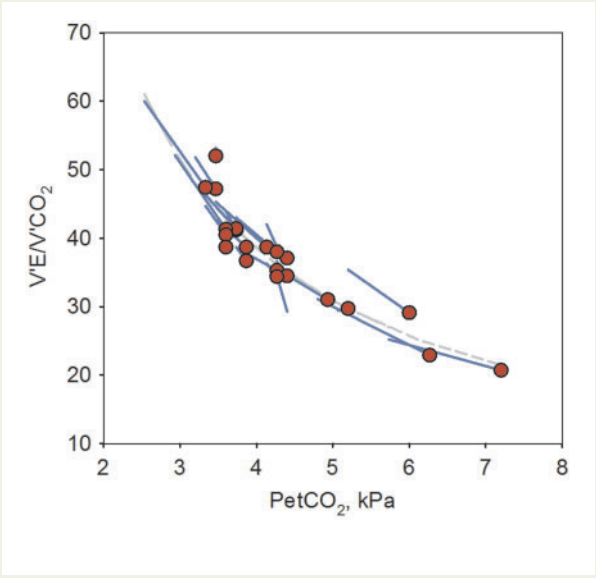

Figure 3 Plot of individual ventilatory equivalents for $V'CO_2$ ($V'E/V'CO_2$) vs. corresponding $PetCO_2$ at end of ramp exercise. Changes induced by hyperoxia are represented by blue lines that start from values measured in normoxia and end in values measured in hyperoxia (FiO_2 0.50, red circles). Hyperoxia shifted the $V'E/V'CO_2$ vs. $PetCO_2$ ratio to more favourable, lower values of $V'E/V'CO_2$ along the long-dashed and short-dashed grey lines that represent least square fits of the rearranged alveolar gas equation through data points from tests with hyperoxia and normoxia, respectively [$V'E/V'CO_2 = a/(PetCO_2 * (1\text{-}VD/VT)$]. As VD/VT ratios were similar in hyperoxia and normoxia the two regression lines are nearly superimposed and the greater ventilatory efficiency in hyperoxia is related mainly to a reduced respiratory drive with higher values of the alveolar and end-tidal PCO_2.

long (mean increase 671 s, 95% CI 392–951, $P < 0.001$, *Figure 2*, Table 3). Under hyperoxia 15/17 patients increased their exercise time by >5% and 10/17 by >50%. $V'CO_2$ at end-exercise under hyperoxia was similar to corresponding values under normoxia, but $V'E/V'CO_2$ at end-exercise was reduced by hyperoxia in association with a lower $V'E$ (*Table 3*, *Figure 2*). Arterial blood gas analysis at end-exercise revealed higher values of PaO_2, SaO_2 and $PaCO_2$ under hyperoxia than normoxia but lower lactate concentrations (*Table 3*, *Figure 2*). The VD/VT ratio was unchanged by hyperoxia. An intention to treat analysis including all randomized patients and entering 0 difference for missing values revealed principally the same results as the per protocol analysis, i.e. a major increase in endurance by hyperoxia vs. normoxia of 515 s (95% CI 260–770, $P < 0.001$). SpO_2 and CTO were both higher under hyperoxia at isotime and end-exercise, whereas QMTO was not significantly different at isotime under hyperoxia compared with end-exercise normoxia. Despite the prolonged exercise time under hyperoxia, patients perceived significantly less dyspnea at end-exercise than under normoxia (*Figure 2*, *Table 3*); Borg scores of leg discomfort did not differ from values under normoxia.

The increase in endurance with hyperoxia was not significantly correlated with any of the physiologic variables tested, nor with sex or 6MWD (Supplementary material online, *Table S2*).

Discussion

The results of the current randomized, sham-controlled, single-blind, cross-over trial in patients with PAH or CTEPH demonstrate that breathing oxygen-enriched air significantly enhanced exercise performance in terms of W_{max} in ramp exercise tests and endurance in submaximal constant load tests. These improvements were associated with a higher $PaCO_2$ at end-exercise, and a reduced $V'E/V'CO_2$ ratio, while the VD/VT ratio remained unchanged. These findings were consistent with a reduction in excessive ventilatory drive by hyperoxia that reduced the ventilatory requirement for CO_2 output. Since hyperoxia led to a higher arterial, cerebral and quadriceps oxygen saturation it may have enhanced exercise performance by promoting availability of oxygen in working muscles and in cerebral motor and sensory neurons while reducing dyspnea perception despite the higher intensity and longer duration of exercise.

The current trial is the first to provide robust, quantitative evidence of the efficacy of breathing oxygen-enriched air in improving exercise performance in patients with PAH/CTEPH. The most impressive effect was observed in tests with submaximal constant load where the endurance was increased more than twice over control values during normoxia. But hyperoxia also increased W_{max} considerably (by 18%). These improvements achieved in patients who were already on PH-targeted medication seem quite relevant for daily life. They support the use of oxygen as an adjunctive therapy during everyday activities.[1] The increases in exercise performance by hyperoxia we observed in PAH/CTEPH patients with a near normal PaO_2 at rest but exercise-induced oxygen desaturation in normoxia exceed those achieved by hyperoxia in healthy volunteers (i.e. 5% increase in W_{max}) showing only minimal exercise-induced desaturation.[25] Thus, the beneficial effect of hyperoxia might be enhanced when there is exercise-induced hypoxaemia in normoxia.

Our data suggest that several mechanisms contributed to the improvements in exercise performance of PAH/CTEPH patients by hyperoxia. A characteristic finding in PAH/CTEPH patients is hyperventilation at rest and an excessive ventilatory response to exercise.[4,6] This has been attributed to increased physiological dead space related to ventilation of lung areas that are poorly perfused due to vessel obliteration and remodelling.[26] However, increased peripheral and central chemosensitivity seems to be another important cause of increased ventilation that may be of particular relevance in PAH/CTEPH patients with severe exercise-induced hypoxaemia due to pulmonary ventilation/perfusion mismatch and right-left shunts through a patent foramen ovale in some patients.[27,28] The increased $PaCO_2$ at end-exercise together with an unchanged VD/VT ratio observed in the current study are consistent with the notion that breathing oxygen-enriched air reduced $V'E$ by reducing hypoxic stimulation of peripheral chemoreceptors. The consecutive rise in $PaCO_2$ and $PetCO_2$ shifted the $V'E/V'CO_2$ vs. $PetCO_2$ relationship to lower ventilatory equivalents for $V'CO_2$. More favourable $V'E/V'CO_2$ vs. $PetCO_2$ relationships were also found in healthy individuals compared with patients with PAH or heart disease known to have an enhanced ventilatory drive.[21] In the current study, the unchanged $V'E$ despite a greater $V'CO_2$ during progressive ramp tests in hyperoxia and the reduced $V'E$ at similar $V'CO_2$ during constant load tests in hyperoxia are consistent with a reduction in excessive ventilatory drive as VD/VT remained constant.

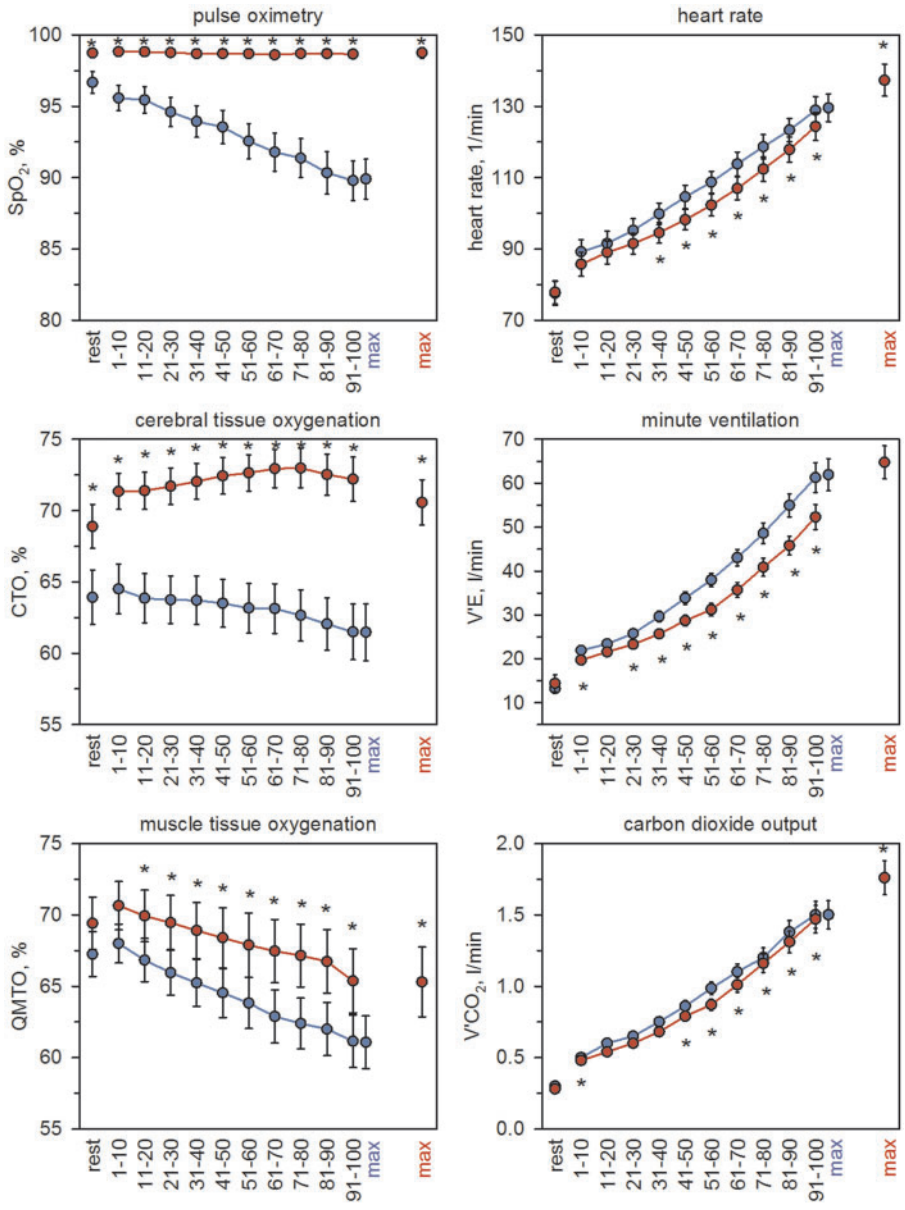

Figure 4 Physiological changes during progressive ramp exercise with blue circles and lines representing normoxia and red circles and lines representing hyperoxia (FiO_2 0.50). The values represent means (±SD) over successive 10% increments of maximal workload (W_{max}) under normoxia, i.e. 1–10%, 11–20% of W_{max} normoxia, etc. The last values (max) represent mean values over the final 30 s end-exercise which occur at a later time with hyperoxia than normoxia.*$P < 0.05$ FiO_2 0.50 vs. FiO_2 0.21.

Hyperoxia was also associated with a lower heart rate at submaximal isoloads/isotimes compared with normoxia presumably related to modulation of the cardiac autonomic control by hyperoxia towards a reduction of the sympathetic overexcitation that has been described in PAH patients[5] and in healthy individuals exposed to hypoxia.[29]

Increasing the arterial PaO_2 by hyperoxia may also have contributed to improved exercise performance by reducing pulmonary vascular resistance and by preventing the exercise-induced drop in arterial oxygen saturation that occurs as a consequence of an inadequate rise in cardiac output and a low mixed venous oxygen saturation in PAH/CTEPH patients. Consequently, the exercise-induced fall in cerebral and muscle tissue oxygenation was also mitigated and delayed by hyperoxia. This might have reduced dyspnea and enhanced the ability of the muscles to perform aerobic work. Thus, during submaximal constant load exercise, the lactate concentration at end-exercise was lower with hyperoxia than normoxia and perceived dyspnea was also lower despite a much longer duration of exercise compared with normoxia. During progressive ramp exercise

Table 3 Constant load bicycle exercise at 75% W_{max} under normoxia and hyperoxia

	Ambient air, FiO_2 0.21, Normoxia	Oxygen enriched air, FiO_2 0.50 Hyperoxia			
	End-exercise	Isotime corresponding to end-exercise time under normoxia	*P*-value	End-exercise	*P*-value
Endurance, s	571 ± 443	571 ± 443	NA	1242 ± 514	<0.001
Work rate, W	86 ± 28	86 ± 28	NA	86 ± 28	NA
Heart rate, bpm	138 ± 17	126 ± 17	0.002	132 ± 16	0.063
Heart rate reserve, bpm	23 ± 17	34 ± 16	0.002	29 ± 17	0.066
Minute ventilation ($V'E$, l/min)	65 ± 19	54 ± 13	0.015	60 ± 13	0.216
Breathing reserve, % MVV	37 ± 17	46 ± 18	0.107	41 ± 18	0.461
Tidal volume, l	1.8 ± 0.7	1.9 ± 0.7	0.464	1.8 ± 0.6	0.825
Breath rate, 1/min	37 ± 10	31 ± 13	<0.001	36 ± 13	0.274
Oxygen uptake ($V'O_2$), l/min	1.4 ± 0.4	NA	NA	NA	NA
$V'O_2$% predicted	88 ± 49	NA	NA	NA	NA
Carbon dioxide output ($V'CO_2$), l/min	1.4 ± 0.5	1.4 ± 0.4	0.855	1.5 ± 0.4	0.285
$V'E/V'CO_2$ at end-exercise	45.8 ± 8.7	37.4 ± 5.7	<0.001	39.6 ± 6.9	<0.001
Death space fraction (VD/VT)	0.47 ± 0.09	NA	NA	0.44 ± 0.09	0.170
End-tidal PCO_2, kPa	3.5 ± 0.6	4.2 ± 0.6	<0.001	4.0 ± 0.8	<0.001
Pulse oximetry (SpO_2), %	88.8 ± 6.9	98.6 ± 1.1	<0.001	98.7 ± 0.9	<0.001
Cerebral tissue SO_2, %	62.0 ± 9.2	68.7 ± 7.5	0.003	68.6 ± 8.1	0.006
Quadriceps SO_2, %	61.3 ± 9.0	65.0 ± 10.3	0.312	66.4 ± 0.4	0.021
Arterial pH	7.35 ± 0.06	NA	NA	7.35 ± 0.07	0.379
PaO_2, kPa	7.6 ± 1.7	NA	NA	32.6 ± 6.7	<0.001
$PaCO_2$, kPa	4.5 ± 0.6	NA	NA	5.2 ± 0.8	0.012
SaO_2, %	88.2 ± 5.3	NA	NA	99.4 ± 0.7	<0.001
Arterial lactate, mmol/l	6.2 ± 1.9	NA	NA	4.2 ± 2.3	0.001
Arterial bicarbonate, mmol/l	19.4 ± 2.1	NA	NA	21.1 ± 3.1	0.020
Borg CR10 dyspnea	5.5 ± 2.1	NA	NA	3.8 ± 2.1	0.002
Borg CR10 leg discomfort	3.8 ± 2.0	NA	NA	3.7 ± 2.7	0.924

Means ± SD, $n = 17$, primary outcome in bold. Individual values were averaged over 30 s; in tests with oxygen enriched air (FiO_2 0.50) isotime refers to the time of end-exercise in normoxia (FiO_2 0.21).
MVV, maximal voluntary ventilation; SaO_2, arterial oxygen saturation by co-oximetry; NA, not available.

with hyperoxia, a higher W_{max} was achieved than with normoxia but lactate concentrations were similar in both conditions.

The relative contribution of the improved oxygen delivery to the brain, heart and working muscles resulting in a better tissue oxygenation, the enhanced ventilatory efficiency and the improved cardiac response reflected by the lower heart rate at isoload under hyperoxia cannot be quantified by our results. The present study includes a limited number of patients with relatively mild PAH/CTEPH and some of them did not undergo constant load exercise tests which limits the generalizability of our results to all PH-patients.

In conclusion, our randomized, sham-controlled trial quantifies for the first time the improvements in exercise performance that can be achieved in PAH/CPETH patients by breathing oxygen-enriched air. Our findings suggest that hyperoxia enhances both maximal cycling performance and endurance in performing submaximal work. It exerts these effects by improving oxygen saturation in the arterial blood, brain and working muscles and by reducing the augmented chemosensitivity that leads to an excessive ventilatory response to exercise. Therefore, our data support the use of oxygen supplementation by patients with PAH/CTEPH during daily activities or training as it may allow them to perform higher levels of physical exercise over a longer duration and reduce dyspnea. The findings expand those from our previous, randomized trial that demonstrated an increase in the 6 min walk distance by nocturnal oxygen supplementation in PAH/CTEPH patients.[15] Further studies should evaluate the effects of long-term oxygen therapy in patients with precapillary PH.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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